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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,625	GLAZIER, ARNOLD	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,6,8-23 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,6,8-23 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

`DETAILED ACTION

1. Claims 4, 5 and 7 have been canceled. Claims 1-3, 6, 8-23 and 27-29 have been amended. Claims 1-3, 6 and 8-29 are pending. Claims 24-26, drawn to a non-elected inventions, remain withdrawn from consideration. Claims 1-3, 6, 8-23 and 27-29 are under consideration.

2. Claims 1-3, 6, 8-22 and 27-29 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 is vague and indefinite because the association between E and T is undefined. It is unclear if ET is restricted only to molecules having a covalent bond between E and T, or if ET encompasses molecules which are not covalently linked. For purpose of examination, both alternatives will be considered.

Applicant argues that the specification teaches that the components of ET are covalently coupled directly or via a linker group and cites page 26. This has been considered but not found persuasive. The cited text is set forth in the specification as a preferred embodiment rather than a limiting definition. Further the MPEP states that

2111.01 [R-3] claims must be given the broadest reasonable interpretation and it is not permissible to read limitations of the specification into the claim during the course of examination. and that

"a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment".

(B) The rejection of claim 1 for the recitation of pharmacological activity is withdrawn in light of applicants amendment which specifies pharmacological activity of ET, rather than E, alone. Applicants arguments regarding the definition of pharmacological activity were not persuasive as the rejection was made because the previous claim language was unclear with regard to what the pharmacological activity was in reference to.

(D) Claim 1 recites "analog of an antibody", "analog of a bispecific antibody" and "component of an antibody". The metes and bounds of an antibody "analog" and "component" are unclear. The convention usage of the word analog implies a functional similarity without structural similarity. The claim requires in part a) a tumor selective targeting ligand which

selectively binds to a target receptor. Selective binding is a property of antibodies. It is unclear how an antibody "analog" can be disclaimed because an antibody analog encompasses all binding agents of non-antibody origin, which is required by part a) of the claim.

Applicant argues that the definition of analog is given by the specification as "a compound of moiety possessing significant structural similarity as to possess substantially the same function". This has been considered but not found persuasive. The specification provides no guidance as to the metes and bounds of what is "significant structural similarity" and "substantially the same" in reference to function. It is unclear how much deviation in structure and in function is tolerated within applicants intended scope of "analog".

(N) Claim 27 is vague and indefinite because the association between E1 and T1 and the association between E2 and T2 which is undefined. It is unclear if ExTx is restricted only to molecules having a covalent bond between Ex and Tx, or if ExTx encompasses molecules which are not covalently linked. For purpose of examination, both alternatives will be considered. The rejection is maintained for the same reasons of record as stated under section A, above.

3. Claims 1-3, 6, 8-23 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

Claim 1 has been amended to recite the limitation "masked" intracellular trapping ligand. Applicant has failed to point out where support for this combination of limitations lies in the 860 pages of the originally filed specification. Thus a rejection of claims 1-3, 6, 8-22 for incorporating new matter is applied.

Claim 12 has been amended to require N3 of zero. Applicant has failed to point out where support for this combination of limitations lies in the 860 pages of the originally filed specification. Thus a rejection of claim 12 for incorporating new matter is applied.

(B)As drawn to inadequate written description of a genus.

Claims 1-3, 6, 8-22 embody anticancer drugs comprising binding ligands which are not antibodies which bind to matrix metalloproteinase, MMP2, MMP3, MMP7, MMP9, MMP12, MMP13, matrilysin or matriptase, said ligands associated in a compound or a complex comprising "masked intracellular transport" ligands, said transport ligands and targeting ligands in association with independent "trigger" molecule which facilitate the release of the ligands after cleavage by intracellular enzymes, said binding ligands, transport ligands and triggers in association with an effector agent, wherein the binding ligands and triggers do not comprise an antibody or an antibody analog.

Claims 23 embodies a compound comprising an effector molecule, and a masked intracellular transport ligand which differ.

Claims 27-29 embody a set of anticancer drugs, each of which comprises effector agents and targeting ligands, wherein the targeting ligands binds to a receptor which includes a matrix metalloproteinase, matriptase, matrilysin, MMP1, 2, 3, 7, 9, 12 and 13., and wherein the second targeting ligand binds to glutamate carboxypeptidase II (PSMA).

Thus the instant claims are drawn to genus of anticancer drugs, said genus limited only by function of binding, triggering and transport. Claims 1-3, 6, 8-22 specify non-antibody ligands, however, this limitations fails to provide any structural attribute for said ligands. It is concluded that the genus encompassed by the claims is highly variant because any structures that comply with the required binding, transport or triggering are tolerated within said genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically

define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. In the instant case the claims are not limited by core structural features commonly possessed by ligands which are not antibodies which bind to the membrane matrix metalloproteinases, matrilysin or matriptase, or core structural feature that act as "triggers" or core structural features that act as "masked transport ligands" or "masked intracellular tapping ligands". The instant specification provides two precise chemical structures for a masked intracellular transport ligand which constitute masked folic acid (for example page 712, lines 4-5) and masked glycinamide ribonculeotide transformylase (page 675, lines 10-13) which binds to the folic acid receptor. the specification fails to provide more than two examples of "masked intracellular transport ligands", or any examples of transport ligands that bind to other receptors apart from the folic acid receptor, or the critical structural unit necessary for a "intracellular transport ligand" for the folic acid receptor or any other internalizing cellular structure. It is noted that the originally filed disclosure fails top provide a single example of a "masked intracellular trapping ligand" or the "trapping ligand" itself.

Claims 1-3, 6, 8-22 of the instant elected Group III requiring a binding agent to a matrix metalloproteinase, matriptase, matrilysin, MMP1, 2, 3, 7, 9, 12 and 13., wherein said binding agent excludes antibodies or antibody analogs. Claims 23 and 27-29 embody the binding agent of matrix metalloproteinase, matriptase, matrilysin, MMP1, 2, 3, 7, 9, 12 and 13., wherein said binding agent excludes antibodies or antibody analogs. The specification provides two precise chemical structures for "MMP selective" ligands (exemplified in compound 2, page 598 and in compound 18, page 668). The description of the two chemical structures fails to adequately describe the genus of MMP, matrilysin and matriptase binding compounds which are not antibody or antibody analogs because said genus tolerates members which differ significantly in structure from the two described ligands.

Claims 27-29 embody a binding agent to glutamate carboxypeptidase II (PSMA). The specification provides a single ligand which binds to PSMA (page 847, in compound A61). This

fails to describe the genus of PSMA binding ligands encompassed by the claims because the genus of PSMA-binding ligands tolerates structures which have not resemblance to the disclosed ligand.

Claims 1-3, 6, 8-10 and 13-22 embody "triggers" which are activated in the cellular milieu. The specification provides a detailed chemical structure for an "intracellular trigger" as exemplified in compound 2, page 598, and an "esterase activated clock-like time delay trigger, also exemplified in compound 2, page 598. These chemical structures fail to adequately describe the claimed genus of intracellular triggers because said genus tolerates structures which are highly different from those described. It is noted that compounds 20 on page 677 also utilizes triggers which are disulfide bonds. However, said esterase delay trigger also fail to adequately describe the highly variant claimed genus of "triggers".

One of skill in the art would reasonable conclude that applicant was not in possession of the broadly claimed genuses encompassed by the instant claims.

4. The rejection of claim 12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record and the additional reasons set forth below.

Claim 12 embodies the compound of claim 4 which ultimately depends on the anticancer drug of claim 1. Claim 12 requires that the effector agent is comprised of a drug that stimulates the immune system. The specification does not teach how to make an anticancer drug comprising a tumor selective targeting ligand which is not an antibody, and which consists of a targeting ligand and a trigger, wherein in vivo modification of said trigger increase the tumor killing activity and wherein in vivo modification of said trigger decreases the tumor killing activity, wherein the effector agent is a drug that stimulates the immune system

Glazier (cited in the previous rejection) teaches how to make the triggers from phosphoramide mustard analogs which increase and decrease the ability of said mustard to evoke cell killing depending on the enzymatic activity contacted by the phosphoramide mustard pro-drug . However, there is no teachings in the specification nor any art of record which would

instruct one of skill in the art on how to construct the chemical trigger necessary for the regulation of cytotoxicity when the effector is an agent which stimulates the immune system. One of skill the art would be subject to undue experimentation to determine the structural attributes necessary for the appropriate "triggers" that would satisfy the requirements of claim 1. Further, one of skill in the art would be subject to further undue experimentation in order to determine how to synthesize the effectors with their appropriate triggers after determining the required structural attributes.

It is noted that the specification contemplates the targeting of "masked antigens", "masked reactive haptens" "ligands that result in the formation of neoantigens", "masked ligands for the delta/gamma T cell receptors", masked ligands that recruit and mobilize macrophages, monocytes and neutrophils" and "masked ligands that recruit and activate NK cells". However, no structures regarding the "making" portion of the ligand, antigen or hapten" are provided, nor the integration of said "masked" moieties into the anticancer ET drug of claim 3 requiring the specific elements N1 through N6. Thus, one of skill in the art would be subject to undue experimentation in order to envision the required structures N1 through N6 for the drug of claim 3 and additionally to envision the "masked" portion of the antigen, hapten or ligand and how to unmask said portion after delivery to the target cells. It is concluded that one of skill in the art would be subject to undue experimentation in order to make such a drug. Further, in the event that one of skill in the art had the masked anticancer drug of claim 12 in hand one of skill in the art would be subject to undue experimentation in order to use said drug to stimulate the immune system in order to provoke an efficacious response in an individual in need thereof. It well accepted in the art that

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity"

and Table 4). The specification has provided evidence that two T-cell clones are able to lyse tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen.

These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

It is well recognized in the art that clinical results on patients do not reflect the results of animal models. For example Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664) teach that encouraging animal model studies lead to clinical trails, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing.

Mohanlal (WO02/40717) teaches that an important reason for the high failure rate in clinical trials is the poor predictive value of currently used screening technologies for biological validation, pharmacological testing, and screening for success or failure of chemical entities and biologicals in clinical trials involving human subjects. Mohanlal teaches these screening technologies are based on in vitro cell-based screening models and in vivo animal models, which often lack or inadequately represent the clinical disease phenotype of the patients in which the tested chemical entities or biologicals are intended to be used in the future.

These references serve to demonstrate that the induction of an efficacious immune response in a human patient is unreliable and the specification has not provided any other non-clinical use for the claimed compound. Thus, without objective evidence in the specification,

one of skill in the art would be subject to undue experimentation in order to use the drug of claim 12 for the treatment of patients.

Claims 1-3, 6, 8-11, 13-23 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification provides chemical structures which comprise an MMP selective ligand or a PSMA selective ligand, a masked intracellular transport ligand in association with an esterase activated clock-like time delay trigger and an intracellular trigger in association with an effector agent (for example, page 845-846 and page 852). the specification suggest a convergent strategy for the synthesis of the chemical compounds, but does not provide any guidance with regard to the physical parameters that govern the synthetic method. Further, the specification suggests that some portions required for the strategy require a multi-step process that appears to be prophetic (for example, page 855 to page 856, line 8). There is no objective evidence that said compounds disclosed by the specification can be isolated and made in useful amounts utilizing the claimed strategy, and further, it would be undue experimentation without reasonable expectation of success to carry out the claimed synthetic strategies without evidence that useable amounts of the desired end-product can be attained. It is recognized in the art, that theoretical strategies for synthesizing a desired organic compound are unreliable. Warren, (Organic Synthesis: The Disconnection Approach, 1982, page xi, lines 9-14 under the heading of "Introduction") teaches that the art of organic synthesis is unreliable, exemplifying that results different from those which are expected are not unusual. Further the title of the book chapter by Jung ("Problem Solving in Organic Synthesis: The False Steps, Failed Pathways and Ultimately Successful Route to the Bottom Half of Ivermectin") are indicative of the problems associated with the synthesis of organic molecules by a method which is novel. The abstract of Wang et al (Journal of Molecular Graphics and Modeling, 2001, Vol. 19, pp. 427-433, lines 5-6 of the abstract) states that organic synthesis is an empirical process. Thus, it is concluded that without an empirical determination of the success of a synthetic route, there is not reasonable expectation of obtaining the desired compound. Given the lack of empirical guidance in the specification,

one of skill in the art would be subject to undue experimentation without a reasonable expectation of success in order to make the disclosed compounds required by the instant claims.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments and arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
7/24/2006